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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PULLIAM, AMY E	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,633	UKAI ET AL.	
	Examiner	Art Unit	
	Amy E Pulliam	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-22,24-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,24-33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of Papers

Receipt is acknowledged of the Request for Extension of Time and the Amendment D, both received by the Office July 14, 2003.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18, 19, 21, 22, 24-28, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/25066 to Depui *et al.* in view of US Patent 6,030,988 to Gilis *et al.*.

Depui *et al.* teach an oral pharmaceutical formulation comprising a proton pump inhibitor, combined with an alkaline substance, protected by coatings. Depui *et al.* disclose that examples of proton pump inhibitors are pantaprazole, lansoprazole, and omeprazole (p 8-11). Depui *et al.* also teach that acceptable alkaline substances can be sodium, potassium, calcium, and magnesium salts of phosphoric and carbonic acid, among others (p 15, l 1-5). In addition, Depui *et al.* give examples which include hydroxypropyl cellulose and crosslinked polyvinypyrrolidone as core ingredients (p 29, l 23 and p 31, l 5). Depui *et al.* also teach that the core formulation will be coated with a separating layer, an enteric coating, and can have additional coatings.

Additionally, applicant's claim 26 claims the drug and excipient mixed in the core, which additional portions of the excipient coated on the outside. Example 4 of the reference teaches crospovidone present in both the core and the second coating layer. These teachings anticipate applicant's claims to a pharmaceutical composition comprising a benzimidizole and an additive (alkaline agent, hydroxypropyl cellulose, or crospovidone), with an intermediate layer, an enteric coating, and optional additional coatings.

Depui *et al.* does not specifically teach all of the possible choices for component B in applicant's claimed composition. However, Depui *et al.* does teach the combination of a benzimidazole with an alkaline agent, such as sodium, potassium, calcium, and magnesium salts of phosphoric and carbonic acid, as well as crospovidone and hydroxypropyl cellulose (p 15, l 1-5). One of ordinary skill in the art would have been motivated to combine any well known alkaline substance with a benzimidazole, based on the teachings of Depui *et al.*. in order to form a formulation for treatment of gastrointestinal disorders.

Depui *et al.* does not teach rabeprazole as a well known benzimidazole. Gilis *et al.* is relied upon for the teaching that omeprazole, rabeprazole, and lansoprazole are all well known proton pump inhibitors (c 5, l 15-18). One of ordinary skill in the art would have used any well known proton pump inhibitor in the composition taught by Depui *et al.*, as the drugs are all from the same family. The expected result would be a successful pharmaceutical formulation, regardless of which proton pump inhibitor is used.

Additionally, Depui *et al.* in view of Gilis *et al.* does not specifically teach sodium hydroxide or potassium hydroxide. However, it is the position of the examiner that based on the teachings of Depui *et al.* to include an alkaline agent, one of ordinary skill in the art would look

to any well known alkaline agent. Absent a showing of criticality, there is no reason to believe that one alkaline agent would behave any differently than another. Therefore, one of ordinary skill in the art would have been motivated to use any alkaline agent in the teachings of Depui *et al.* with the expected result being a successful formulation of a benzimidazole. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 20, and 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Depui *et al.* in view of Gilis *et al.* as applied above, and further in view of US Patent 5,708,017 to Dave *et al.*. Depui *et al.* in view of Gilis *et al.* are described above as teaching a formulation comprising a benzimidazole, an alkaline agent, or an excipient such as HPC or crospovidone, an intermediate coating, an enteric coating and optional additional coatings. Depui *et al.* in view of Gilis *et al.* do not teach that the composition have a moisture resistant coating. Dave *et al.* teach of an oral pharmaceutical composition containing a proton pump inhibitor. Further, Dave *et al.* teach the proton pump inhibitors are known in the pharmaceutical art to be very acid labile and therefore, must be enteric coated. Dave *et al.* also teach that this enteric coating causes a great problem with moisture sensitivity. It is the position of the examiner that one of ordinary skill in the art would have been motivated to make one of the additional coatings allowed in the Depui composition a moisture resistant coating based on the teachings of Dave *et al.*. The expected result would be a successful enteric coated formulation which is resistant to moisture. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's amendments have been fully considered but are not found to be persuasive. Applicant points out that claim 34 has been rewritten as two independent claims, 35 and 36. Claim 35 requires a ratio of 1 part drug to 0.01 to 0.5 parts NaOH. Claim 36 requires 1 part drug, 0.01 to 0.5 parts NaOH and 0.5 to 5 parts crospovidone. The examiner has compared these ratios to the data in the previously submitted declaration, in search of unexpected results. The declaration teaches that the best ratio of alkaline agent to drug is 10: 0.5, however, this particular ratio is only present in claim 37. Applicant's experimental data is presented to show that a change in ratio between alkaline agent and active agent can greatly impact the success of the formulation and its lack of degradation. However, Applicant has claimed ratios which are not supported by unexpected results in the declaration. There is no data to show that the ratios claimed in claims 35 and 36 will achieve the same results as the range claimed in claim 37. Furthermore, evidence would suggest that the different ratios claimed would not have the same results, based on the great difference noted with a change of 0.5 NaOH to 1.0 NaOH to 20.0 NaOH. [See experiments 1-4 of the declaration]. In order for Applicant to assert unexpected results for the instantly claimed ranges, the examiner suggests that Applicant present data which shows the upper and lower limits of the claimed ratios. Additionally, it would be beneficial to compare these upper and lower limits to amounts just outside the claimed ratio, to show that the unexpected results occur specifically within the claimed ratios.

The examiner reasserts her position on the remainder of the claims, as no amendments have been made to these claims.

First, Applicants have prepared several compositions, each containing a different alkaline substance, in an effort to show unexpected results with the use of sodium hydroxide. Most of Applicant's examples use 10.0 g sodium rabeprazole and either 0.5 g or 20.0 g alkaline substance. Applicant's discuss in the declaration that the formulation comprising 20.0 g alkaline substance could not be made into a tablet, and therefore there is no data concerning this formulation. However, the ratio of 1:2 is still present in many of the claims.

Second, Applicant's have provided no specificity for the data recorded in tablets 2-4. For example, it is not clear to the examiner what the numbers in tablet 2 represent. Applicant has stated that a change in color indicates declaration of the active agent, but without units it is impossible to determine what the table really proves. It is unclear if this is even a patentable difference. Furthermore, none of the data in the tables is expressed with statistical analysis. This makes it impossible to determine how scientifically significant any of the numbers are.

Third, there are many instances throughout the tables, where a substance other than sodium hydroxide has a better result. For example, regarding table 1, experiment 12, using calcium hydroxide, has a smaller color change than both experiments 2 and 3, for both the 60° and the 40° tests. Applicant's discuss this, and dismiss it because "more than 1.20 parts by weight of the alkaline agents were necessary for 10 parts by weight of sodium rabeprazole to inhibit color change." This argument is not found persuasive because Applicant's allow for a 2:1 ratio of drug to alkaline agent in the instant claims. Furthermore, the tablets show 20.0 g of alkaline substance was used in example 12, not more than 20.0 g. Additionally, many of the other experiments have values which are less than or very close to the values shown for experiments 2 and 3. Without statistical analysis and standard deviation, it is impossible to

determine if Applicant has indeed provided unexpected results. This remains true for tables 2, 3, and 4. It is unclear to the examiner how Applicant can argue unexpected results when there are other alkaline substances which appear to have better results than the alkaline substance claimed by Applicant.

Fourth, Applicant's instant claims recite "rabeprazole or an alkali metal salt thereof," however, the data presented only applies to the salt form of the drug. It is asserted by the examiner that the drug in base form may behave quite differently than the drug in its salt form. Applicant's have stated that they do not have data for the free base form of rabeprazole, but that one skilled in the art would expect the free base to perform no differently than the salt form. The examiner respectfully disagrees. Based on the effect the presence of an alkaline agent has on these substances, it remains the position of the examiner that the salt and free base forms may behave very differently. Therefore, in order for the scope of the declaration to be commensurate with the scope of the claims, data should be provided showing any unexpected results found using the base form of rabeprazole. Absent any such showing, it is recommended that Applicant cancel the limitation drawn to the free form of the active agent upon response to this action.

Applicant's have a particular ratio recited in the instant claims. Furthermore, Applicant's have attempted to show in their data that the ratio between drug and alkaline substance can make a difference in the unexpected results. However, Applicant's have not provided data which falls at the low end of their claimed range. It is suggested that data be supplied which is commensurate in scope with both the upper and the lower limit of the claimed ratio range.

Lastly, although claim 37 recites the specific ratio between active and alkaline agent which is shown in the declaration, the examiner still has problems with the presentation of the

data. As discussed above, without a showing of statistical analysis, it is impossible to determine if the results shown in the table are significant. Table 4 shows degradation product amount, in percent. Many of the numbers presented in this table are close, and without standard deviation, it is impossible to determined the significance. Appropriate action is recommended.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E Pulliam whose telephone number is 703-308-4710. The examiner can normally be reached on Mon-Thurs 7:30-5:00, Alternate Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A. Pulliam
Patent Examiner
Art Unit 1615
September 11, 2003

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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